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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,745	06/24/1998	SUDHIR AGRAWAL	IDRA-740US1	3401

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/103,745	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 16-18* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 6/16/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2/12/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Also acknowledged are Applicant's amendments to the claims. With entry of the amendment filed on 6/16/08, claims 1, 3-5, and 16-18 are pending in the application. Claims 3-5 remain withdrawn. Claims 1 and 16-18 are currently under examination.

This application contains claims that are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim interpretation

The specification teaches at page 8 that for purposes of the invention the term "phosphorothioate oligonucleotide" means an oligonucleotide containing at least one phosphorothioate internucleoside linkage.

The specification teaches at page 8 that "a CpG dinucleoside is "modified" if it is altered from the unmodified CpG dinucleoside such that it confers upon the oligonucleotide a reduced ability to cause splenomegaly and platelet depletion."

The specification teaches at page 11 that "A 2'-0-substituted CpG is a CpG dinucleoside in which the 2' position of the pentose moiety is substituted." The specification further states that "Most preferably, the 2'-0-Substituted CpG is a 2'-0-methyl cytosine containing CpG, or a 2'-0-methyl guanosine containing CpG or both."

Accordingly, as amended on 6/16/08, the instant claims embrace oligos having one or more phosphorothioate linkages and one or more CpG dinucleotides in which the C or G or both in each of said dinucleotides is 2'-O substituted.

Oligos meeting these structural limitation are considered to have the biological properties recited in the claims, as evidenced by the claims. From a practical standpoint, the Office is not in a position to test oligonucleotides in the prior art meeting the structural limitations of the claims to ensure such oligos also possess each physical and chemical property recited in the claims. As a chemical and its physical/biochemical properties are inseparable, there is sufficient reason to believe an oligonucleotide having each of the structural characteristics recited in the claims would necessarily also have the physical and chemical properties inherent to such compounds, such as those properties recited in the claims. Burden is shifted to applicant to show otherwise. MPEP 2112.

Thus, for purposes of the prior art rejections below, functional limitations such as "reduced side effects" and "fewer side effects" are considered to represent nothing more than inherent properties of modified CpG-containing phosphorothioate oligonucleotides. While the prior art may not have recognized this property at the time, it is not necessary under 35 USC 102 or 103 that all properties inherent to a prior art compound be disclosed along with compound, so

long as the compound and a method for said compound was disclosed. The following case law cited in the MPEP 2112 and 2145 is believed to be relevant:

1. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).
2. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).
3. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979).

As shown by the following prior art rejections, modified CpG-containing phosphorothioate antisense oligonucleotides, wherein all CpG dinucleotides present in the oligo were modified, and methods for using said oligonucleotides in mammals were known in the prior art.

The claims require no minimum level of gene expression inhibition. Thus, the limitations "for inhibiting specific gene expression" and "for which inhibition of expression is desired" in claims 1 and 16 embraces any level of inhibition. Claims 17 and 18 require no inhibitory activity, but only that the administered oligonucleotide be complementary to a particular target.

The limitations "reduced side effects" and "fewer side effects" does not require the complete absence of side effects. Any reduction, even a fraction of 1%, relative to the unmodified oligonucleotide is within the scope of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kawasaki et al. (1993) *J. Med. Chem.* 36:831–841.

Kawasaki et al. disclose a 15-nucleotide CpG-containing antisense oligonucleotide comprising a phosphorothioate backbone in which each CpG is 2'-O-methyl modified that is specific for human papilloma virus genome (see oligo #12 in Table 1, page 833).

Compositions thereof are also disclosed and tested (see pages 833–840).

Although, Kawasaki et al. do not teach that the disclosed oligo inhibits gene expression with "reduced side effects," the oligo disclosed meets the structural limitations of the claim and would necessarily possess this property.

"There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference." (MPEP 2112).

Accordingly, Kawasaki et al. anticipate the instant claim.

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Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Monia et al. (1993) *J. Biol. Chem.* 268:14514-14522.

Monia et al. disclosed the benefits of using chimeric phosphorothioate 2'-O-methyl subsitituted oligonucleotides that contain between 5 and 9 centered 2'-deoxy residues flanked by 4 to 6 2'-O-methyl substituted nucleotides on the 5' and 3' ends, or wings (pp. 14516-14522; Fig. 1 and 4). Such compounds are said combine the favorable aspects of PS-oligonucleotides (RNase H activation) and 2'-O-methylribonucleotides (nuclease and duplex stability), resulting in increased potency (page 14514-5 and 14520-2).

In one exemplary embodiment (Fig. 1, Fig. 3, and Fig. 4), Monia et al. disclosed a phosphorothioate CpG-containing oligonucleotide complementary to a human Ha-ras gene, having a 3-nucleotide deoxy gap in which each CpG dinucleotide comprises at least one 2'-O-methyl modified C or G or both (see the oligo fourth from the top in Fig. 1). This oligonucleotide, which is complementary to a gene or RNA transcribed from said gene, and is shown to support RNase H-mediated mRNA cleavage, albeit at a lower efficiency relative to other gapped oligos (Figs. 3 and 4, and discussion at page 14517), meets the structural requirements to the claims. Absent evidence to the contrary, the oligo would necessarily have reduced side effects relative to the corresponding unmodified oligo. MPEP 2112.

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Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Monia et al. (US Patent 5,563,255).

Monia et al. disclosed a 2'-O-methyl modified CpG-containing phosphorothioate antisense oligonucleotide, 20-nucleotides in length, complementary to the human c-raf gene for

inhibition of said gene in cells in vitro and in vivo (see ISIS 6712, 6720, 6717, 6729, and 9271 in Tables 2-5, cols. 10-15; and disclosure cols. 1-20). The oligonucleotides are chimeric or gapped derivatives of the unmodified ISIS oligo 5132 (SEQ ID NO:8) shown in Table 1. Oligonucleotide ISIS 6720 (Table 4), for example, is a uniformly PS modified oligonucleotide, comprising a 6-nt deoxynucleotide gap flanked by 7-nt 2'-O-methyl modified wings on either side. The oligo has a single CpG dinucleotide on the 5' side of the deoxy gap within the 7-nt 2'-O-methyl modified segment. Accordingly, ISIS 6720 meets each of the structural limitations of the claim, a do ISIS 6717 and 6729. All three oligos are said to be preferred for inhibiting c-raf mRNA (see cols 11-13). All three oligos were said to inhibit c-raf expression by at least 70% when tested (col. 11).

Accordingly, Monia et al. anticipate the instant claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawasaki et al., as applied to claim 1 above, in view of Agrawal et al. (WO 94/01550) and Shillitoe et al. (1994) *Cancer Gene Therapy* 1:193–204.

Kawasaki et al. is relied on for the reasons given above.

Kawasaki et al. did not teach steps for administering Oligo #12 of Table 1 to a mammal.

However, Kawasaki et al. explicitly recognized the antisense, Rnase H activity of each of the chimeric oligos disclosed therein, including the 2'-O-methyl modified, papilloma virus-specific oligo 12 set forth in Table 1, and, on the basis of their studies, suggest applying the oligos against biological targets (page 837, right column).

Agrawal et al. set forth methods and materials for making and using self-stabilized, phosphorothiote antisense oligonucleotides against virtually any known viral or cellular gene, and specifically taught and suggested methods for administering such oligos to animals and humans for therapeutic purposes to treat a diseased human or animal in which the disease results from infection with a virus or pathogenic organism, or from the abnormal expression or produce of a cellular gene. The method comprises administering self-stabilized oligonucleotides according to the invention in a pharmaceutically acceptable carrier to the diseased human or animal (page 18 and claims 18-20).

Shillitoe et al. teach that papilloma viruses are etiological agents of cancer, and are often present in many cervical and oral cnacers.

It would have been obvious to one of skill in the art at the time the instant methods were invented to have made and administered the Kawasaki et al. oligos according to the methods taught by Agrawal et al.

One would have been well motivated and have had a reasonable expectation of success given that Kawasaki et al. taught that the oligos disclosed therein possess antisense activity against human papilloma virus, given that Agrawal et al. taught that chemically modified, self-stabilized antisense oligos are more resistant to nuclease degradation and more potent than conventional single-stranded antisense oligonucleotides, that such oligos are effective for treating viral infections, and that such oligos may be administered to humans for the treatment of viral infections, and given that Shillitoe et al. taught that papilloma viruses may be the underlying cause of some forms of human cancer.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

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Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (US Patent 5,563,255) as applied to claim 1 above, and further in view of Monia et al. (US Patent 5,563,255).

Monia et al. is relied on for the reasons given above in the rejection of claim 1 under 35 USC 102(e).

Monia et al. do no specifically exemplify the use of the cited oligonucleotides in a mammal or individual with a disease.

However, Monia et al. taught using said chimeric anti-c-Raf antisense oligonucleotides for research and therapeutic purposes in cells in vitro and in vivo to inhibit the expression of c-raf in cells in culture and in mammals (cols. 1-20). Monia et al. taught the association between c-raf expression and cancer, or abnormal cell proliferation (cols. 1-5). Monia et al. taught that oligonucleotides of their invention may be used to inhibit gene expression in cells in culture and in animals, as is common in research and development work investingating oncogenes (see examples in cells and nude mice at columns 15-20). Monia et al further taught the c-raf antisense oligonucleotides may be used as therapeutics and formulated for oral, intravenous, suncutaneous, or intraperitoneal administration (col. 8 and see examples at cols. 15-20). Monia et al. showed that ISIS oligonucleotides 5132, a PS antisense lacking 2'-O-methyl modifications but otherwise identical to the chimeric oligos cited in the 35 USC 102 rejection above, may be administered by intraperitoneal injection to nude mice having T24 human bladder carcinoma tumor xenografts (cols. 17 and 18). The oligo was said to inhibit tumor growth in said mice (cols. 13 and 14). See also other in vivo exemplary embodiments of colon cancer xenografts in mice.

Accordingly, it would have been obvious to one of skill at the time of invention, that Monia et al. clearly contemplated and appreciated that the chimeric, 2'-O-methyl modified phosphorothioate anti-raf oligonucleotides disclosed therein could be used in mice/xenograft models to inhibit tumor cell growth and investigate c-raf expression as it relates to tumor cell growth in vivo. As each of the olignucleotides cited above in the 35 USC 102 rejection were clearly certified to be effective for inhibiting c-raf expression in tumor cells in culture, and in view of the exemplary embodiment of ISIS 5132, representative of the SEQ ID NO:8 and modified variants thereof, demonstrating its use in vivo, one of skill would have reasonably

predicted that each of ISIS oligos 6720, 6717, and 6729 could be used in the same manner to produce similar if not superior results in a nude mouse or individual comprising said tumor cells.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Applicants' Arguments

Applicants' arguments presented on 6/16/08 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner AU1635
August 29, 2008

/Sean R McGarry/

Primary Examiner, Art Unit 1635